REMARKS

Claims 7-9 and 12-15 are now currently pending in the present application. Claims 1-4, 6, 10 and 11 have been cancelled herein. New claims 12-15 have been added, for which support may be found in the specification, at least, at pages 19-20. No new matter has been added by way of the present claim amendments.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-6 stand rejected, as failing to comply with the written description requirement because of the addition of new matter. Claim 10 stands rejected, as failing to comply with the written description requirement because of the addition of new matter.

Claims 1-4, 6 and 10 have been cancelled herein. Therefore, the outstanding rejections are rendered moot. Withdrawal thereof is respectfully requested.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-4, 6, 10 and 11 stand rejected under 35 U.S.C. 112, second paragraph.

Claims 1-4, 6, 10 and 11 have been cancelled herein. Therefore, the outstanding rejections are rendered moot. Withdrawal thereof is respectfully requested.

However, Applicant believes that the Examiner has misunderstood the scope of the present invention. Therefore, in an effort to avoid having the indefiniteness rejection applied to the remaining claims, Applicant has the following comments.

In the previous Office Action, at paragraph 20, the Examiner stated that if the claim recites that the composition "consists essentially of EPA", and it contains an antioxidant, the antioxidant can act as an active agent and an excipient. The Examiner appears to be taking the position that this language is somehow inconsistent.

However, Applicant respectfully submits that the Examiner is mischaracterizing the claims. The claims do not recite the presence of an antioxidant. Moreover, the specification at page 14, lines 3-10, explains that an antioxidant is merely "desirable", not required.

The composition of the present invention as described in the Examples of the specification in which the effect for varicose veins of lower extremities can be observed comprise of only EPA-E as the effective component. The other inactive ingredients, such as tocopherol, can be properly characterized as part of the claimed "pharmaceutically acceptable carrier." However, in an effort to advance prosecution of this application, new claims 14 and 15 have been added in which tocopherol is positively claimed as an ingredient. Additionally, Applicant submits **Mochida Pharmaceuticals EPADEL Product Information** which demonstrate that *dl*-α-tocopherol (antioxidant) is an inactive ingredient. Therefore, the tocopherol does not "materially affect the basic and novel characteristics of the invention." *PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998).

Therefore, Applicant respectfully submits that there is no indefiniteness in the scope of the presently claimed invention.

Rejections under 35 U.S.C. §102, Anticipation

Claim 10 stands rejected under 35 U.S.C. §102(b) as being anticipated by EP 0 404 300 to Yazawa et al. (hereinafter "Yazawa").

Claims 1-4 and 6-11 stand rejected under 35 U.S.C. §102(b) as being anticipated by USP 5,604,216 to Horrobin (hereinafter "Horrobin").

Claims 7-11 stand rejected under 35 U.S.C. §102(b) as being anticipated by WO 01/84961 to Kiliaan et al. (hereinafter "Kiliaan").

Claims 7-11 stand rejected under 35 U.S.C. §102(b) as being anticipated by USP 5,776,978 to Bruzzese et al. (hereinafter "Bruzzese").

Claims 1-4, 6, 10 and 11 have been cancelled herein. Therefore, the outstanding rejections with regard to these claims are rendered moot. With regard to the rejection of claims 7-9, Applicant respectfully traverses.

Horrobin

The Examiner alleges that Horrobin discloses the use of EPA (eicosapentaenoic acid), particularly the ester form, in a suitable diluent or carrier. The Examiner further alleges that Horrobin teaches that fatty acids including EPA have therapeutic value in a number of disorders specifically addressing the cardiovascular system and peripheral arterial disease, which encompasses varicose veins. Applicant respectfully disagrees.

Horrobin provides a general disclosure of the treatment of many conditions, of which the treatment of varicose veins is not disclosed. Horrobin does not provide any example of a composition for the treatment of varicose veins consisting essentially of EPA-E (eicosapentaenoic acid ethyl ester) and a pharmaceutically acceptable carrier.

Accordingly, Applicant requests reconsideration and withdrawal of the outstanding rejection.

Kiliaan

The Examiner alleges that Kiliaan discloses the use of EPA for vascular disorders and further for varicose veins. However, Applicant respectfully disagrees.

Kiliaan describes that the mixture of

a) polyunsaturated fatty acids,

b) phospholipids and

c) compounds which are a factor in methionine metabolism can prevent and treat vascular disorders, and further describes EPA as an example of polyunsaturated fatty acids, as well as varicose veins as an example of vascular disorders.

However, Kiliaan and the present invention are different in that Kiliaan describes the mixture of three fractions while the present invention is directed to a method of treating varicose veins consisting essentially of EPA-E as the effective component. Thus, Kiliaan cannot anticipate the claimed invention because Kiliaan includes many additional components which materially affect the composition.

Moreover, Kiliaan provides no particular data demonstrating that the above mixture can prevent and treat vascular disorders. Nor does Kiliaan include data to show the effectiveness in preventing and treating varicose veins. On the other hand, the present invention is distinctive in having particularly demonstrated that the therapeutic agent consisting essentially of EPA-E as the effective component has effects in treating varicose veins of human lower extremities (See the Examples of the present application).

Accordingly, Applicant requests reconsideration and withdrawal of the outstanding rejection.

Bruzzesse

The Examiner alleges that Bruzzesse discloses the use of EPA for cardiovascular conditions and atherosclerosis, while the Mayo Clinic sheets show that the cardiovascular conditions encompass varicose veins. Applicant respectfully disagrees.

Bruzzesse describes that the combination of polyunsaturated fatty acids and 10-40% by weight of antioxidant vitamins is useful for preventing and treating cardiovascular diseases and the like, and further describes EPA and their esters as examples of the polyunsaturated fatty acids. However, Bruzzesse and the present invention are different in that Bruzzesse describes

the synergistic effect of the above combination, while the present invention directed to a method of treating varicose veins consisting essentially of EPA-E as the effective component. Thus, Bruzzesse cannot anticipate the claimed invention because Bruzzesse includes many additional components which materially affect the composition.

In addition, Bruzzesse discloses that the above combination synergistically suppresses the oxidation of LDL, however, it does not show any particular data regarding that the suppression is effective for treating varicose veins. On the other hand, the present invention is distinctive in having particularly presented that a composition consisting essentially of EPA-E as the effective component has effects in treating varicose veins of human lower extremities (Examples of the present application). Accordingly, Applicant requests reconsideration and withdrawal of the outstanding rejection.

In view of the foregoing, Applicant believes the pending application is in condition for allowance. A Notice of Allowance is earnestly solicited.

Conclusion

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Monique T. Cole, Reg. No. 60,154 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: February 19, 2008

Respectfully submitted,

By M. J. Murphy for MTC
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Attachment: Mochida Pharmaceuticals EPADEL Product Information

Revised: April 1998 (1st version of new form)

Standard Commodity Classification No. of Japan
873399
872189

- An EPA Preparation -

EPADEL® CAPSULES 300

<Soft Capsules of Ethyl Icosapentate>

Designated drug

Storage
Store at room temperature. Precautions: Store in high-temperature-proof, moisture-proof and light resistant containers.

Expiration date
This drug should be used before the expiration date indicated on the package and label.

Approval No.	(02AM) No.0642
Date of listing in the NHI reimbursement price	May 1990
Date of initial marketing in Japan	June 1990
Date of latest reexamination	March 1998
Date of latest approval of indications	October 1994

CONTRAINDICATIONS (EPADEL Capsules 300 is contraindicated in the following patients.)

Hemorrhaging patients (e.g. hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoprysis, vitreous hemorrhage, etc.) [Hemostasis may be more difficult.]

DESCRIPTION

Brand name	EPADEL Capsules 300	
Ingredient/ content	Content per capsule 300 mg of ethyl icosapentate (EPA-E)	
Inactive ingredients	*dl*-α-tocopherol	
	Capsule composition	ethyl parahydroxybenzoate propyl parahydroxybenzoate
Dosage form	Light yellow, clear, soft capsules	
Appearance		
Size (mm)	approx.18 approx.7	
Identification code	MO 207 (Labeled on PTP sheets)	

INDICATIONS
DOSAGE AND ADMINISTRATION

Indications	Dosage and Administration
Improvement of the associated ulcer, pain and coldness in arteriosclerosis obliterans	Usually for adults, administer orally 600 mg of ethyl icosapentate (2 capsules) 3 times daily, immediately after meals. The dose may be increased or decreased, depending on the age and condition of the patient.
Hyperlipidemia	Usually for adults, administer orally 600 mg of ethyl icosapentate (2 capsules) 3 times daily, immediately after meals. In the case that triglyceride level is abnormal, the dose may be increased up to 900 mg (3 capsules) 3 times daily, depending on severity.

PRECAUTIONS

1. Careful Administration (EPADEL Capsules 300 should be administered with care in the following patients.)
   (1) Patients in menstruation
   (2) Patients with hemorrhagic tendency
   (3) Patients scheduled for surgery
   [(1)~(3) Hemorrhage may be exacerbated.]
   (4) Patients on medication with anticoagulants or antiaggregators of platelets (See "Drug Interactions")

2. Important Precautions
   (1) To use EPADEL Capsules 300 for improvement of the associated ulcer, pain and coldness in arteriosclerosis obliterans, observe the course closely, and if the drug is not responded to, discontinue the use of the drug and switch to another therapy. It is also advisable to perform periodical hematologic testing during the administration of EPADEL Capsules 300.
   (2) To use EPADEL Capsules 300 for Hyperlipidemia, the following should be taken into consideration:
      1) Use of EPADEL Capsules 300 should be considered only after hyperlipidemia has been established by a thorough examination.
      2) Prior to EPADEL Capsules 300 therapy, diet therapy, fundamental treatment for hyperlipidemia, should be given, and an exercise therapy and a reduction of ischemic heart disease risks, such as hypertension and smoking should be considered.

3) During the treatment, the blood lipid level should be measured periodically. If no response to the treatment is obtained, the EPADEL Capsules 300 therapy should be discontinued.

3. Drug Interactions

Precautions for coadministration (EPADEL Capsules 300 should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Anticoagulants (e.g. warfarin, etc.) Antiaggregators of platelets (e.g. aspirin, indomethacin, ticlopidine hydrochloride, cilostazol, etc.)	Hemorrhagic tendency may be increased.	Since ethyl icosapentate has an anti-platelet effect, coadministration with anticoagulants and antiaggregators of platelets may increase hemorrhagic tendency.

4. Adverse Reactions

Adverse reactions to EPADEL Capsules 300 were reported in 439 of 12,007 patients treated (3.7%). The following adverse reactions are reported on the basis of spontaneous reports, and the number of patients and incidence are unknown. (As of September 1997)

Adverse Reaction

If any of following signs is observed, appropriate measures must be taken depending on condition of the patient.

	5% > ≥0.1%	<0.1%	Incidence unknown
Hypersensitivity [1]	Rash, itching, etc.		
Hemorrhagic tendency [1]		Subcutaneous hemorrhage, hematuria, etc.	
Hematological	Anemia, etc.		
Gastrointestinal	Nausea, gastric discomfort, diarrhea	Vomiting, anorexia, constipation, etc.	
Hepatic [1]	Increased GOT (AST) and /or GPT (ALT)	Increased ALP, etc.	Icterus
Others	Increased CK (CPK)	Headache, dull, dizziness, giddiness, sleepiness, insomnia, hot flush, feeling of warmth, fever, heart pounding, edema, numbness, arthralgia, pollakiuria	Gynaecomastia

Note 1) If there is any such manifestation, discontinue the use of EPADEL Capsules 300.

2) Observe the patient closely, and if any such manifestation occurs, discontinue the use of EPADEL Capsules 300 and appropriate measures must be taken.

5. Use during Pregnancy, Delivery or Lactation

(1) As the safety of EPADEL Capsules 300 in pregnancy has not been established, administer EPADEL Capsules 300 to pregnant women or women suspected to be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

(2) It is advisable not to administer the drug to nursing women, but when administration is judged necessary women should be advised to stop nursing. [Animal studies (rats) have shown that EPADEL Capsules 300 is excreted in breast milk.]

6. Pediatric Use

The safety of EPADEL Capsules 300 in children has not been established. (No clinical experiences.)

7. Precautions concerning Use

(1) Cautions for use

1) As EPADEL Capsules 300, if administered on an empty stomach, is poorly absorbed, administer the capsules immediately after meals.

2) Do not chew the capsules.

(2) At the time of delivery of drugs

For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]

8. Other Precautions

It has been reported that in case of the patient with a poorly controled high blood presure, when co-administered with other antiplatelet agents, the cerebral hemorrhage occured.

PHARMACOKINETICS

1. Plasma levels

Oral administration of a single dose of 1,800 mg or 2,700 mg of EPADEL Capsules 300 to healthy adult men immediately after a meal was followed by the occurrence of a peak plasma level of the drug 6 hours later, and the plasma level returned to approximately the level before the administration 24 hours later. Daily oral administration of 600 mg or 900 mg of EPADEL Capsules 300 3 times a day for 4 weeks, immediately after meals, resulted in the plasma level of EPADEL Capsules 300 reaching a plateau in about one week from the first administration.

2. Excretion (reference)

Oral administration of ^{14}C-EPA-E to male rats was followed by urinary excretion of 2.7% and the fecal excretion of 16.7% of the administered dose during 168 hours after the administration. Also, 44.4% of the administered radioactivity was excreted in the expired air. [1]

CLINICAL STUDIES

1. **Arteriosclerosis obliterans**
In clinical studies[2-5] of EPADEL Capsules 300 including double-blind comparative studies, the effectiveness of the drug in treating patients with arteriosclerosis obliterans, associated with ulcer, resting pain and coldness due to peripheral circulatory disorder, was such that the effectiveness, made up of "moderately effective" and better ratings, was 55.9% (52/93 patients), and the effectiveness, made up of "fairly effective" and better ratings, was 88.2% (82/93 patients).

2. **Hyperlipidemia**
In clinical studies [6-11] of EPADEL Capsules 300 including double-blind comparative studies, the overall improvement rate of the drug in treating patients with hyperlipidemia, was such that the effectiveness, made up of higher improvement, was 43.8% (163/372 patients), and the effectiveness, made up of moderate improvement or higher improvement, was 68.0% (253/372 patients).
In long term administration studies (24-52 weeks) [7-11] total serum cholesterol (before administration, higher than 220mg/dL, 137 patients) decreased 3-6%, and serum triglyceride (before administration, higher than 150mg/dL, 97 patients) decreased 14-20%, thus, indicating the drug's efficicy in reducing these levels.

PHARMACOLOGY

1. **Serum lipids-lowering effect**
   (1) EPA-E significantly decreases total serum cholesterol level and/or serum triglyceride level of hyperlipidemic patients. [6-12]
   (2) The effect of decreasing blood lipid levels is shown in hyperlipidemic animals (rats, rabbits) fed on high-cholestorol food, hyperlipidemic rats fed on food including casein or fed on triton and in animals (rats, hamsters) fed on normal food. [12-15]
   (3) When EPA-E is administered orally to rats, EPA content in lipoprotein increases and the elimination of lipoprotein in blood is enhanced. [16, 17]
   (4) EPA-E inhibits the intestinal cholesterol absorption and the hepatic cholestrol biosythesis, and also enhances hepatic biliary secretion(rats).[16]
   (5) EPA-E inhibits the intestinal triglyceride absorption, the hepatic triglyceride biosythesis, the hepatic secretion, and also increases the plasma lipoprotein lipase activiation (rats).[17,18]

2. **Anti-platelet effect**
   (1) EPA-E inhibits the platelet aggregation induced by various platelet aggregators, and, likewise, inhibits platelet viscosity in patients with various thrombotic and arteriosclerotic diseases.
   (2) It appears that EPA-E inhibits competitively the metabolism of arachidonic acid released from the platelet membrane, chiefly by increasing the EPA content of phospholipids in the platelet membrane thereby inhibiting the formation of thromboxane A_2 and consequently inhibiting platelet aggregation.
   (3) EPA-E inhibits the platelet aggregation induced by collagen (rabbits, *ex vivo*).[19]
   (4) EPA-E inhibits the platelet aggregation induced by collagen, ADP or arachidonic acid in rats, rabbits and humans (*in vitro*).[19]
   (5) EPA-E has proved not to change or to increase the formation of prostacyclin-like substances in the walls of rat thoracic aorta.

3. **Arterial elasticity-maintaining effect**
   (1) EPA-E inhibits the decreased elasticity of isolated aorta from rabbits fed on high-cholesterol food, keeping the aorta as elastic as those from rabbits fed on normal food.[21]
   (2) EPA-E inhibits the increase in pulse wave velocity (PWV) in the thoracic aorta and the femoral artery of rabbits fed on high-cholesterol food to the extent that it is comparable to the velocity in the rabbits fed on normal food.[22]
   (3) EPA-E inhibits the decrease of density of medial smooth muscle cells, decrease of elastin content, and the accumulation of free cholesterol in the smooth muscle of aorta specimens prepared from rabbits fed on high-cholesterol food.[23] EPA-E also inhibits the proliferation of the intimal smooth muscle cells.

4. **Effects on models for various pathologic conditions**
EPA-E, when administered orally, prevents the sudden death due to a formation of thrombus by intravenous injection of arachidonic acid (rats).[23] It also inhibits the formation of thrombus in thrombotic occulson due to arteriovenous shunting (rats)[25] and in ellagic acid-induced thrombosis (rabbits)[24], and also prevents the progress of peripheral gangrene (rats) induced by lauric acid.[26]

PHYSICOCHEMISTRY

Nonproprietary name:
Ethyl icosapentate (JAN), Icosapent (INN)

Chemical name:
ethyl all-*cis*-5, 8, 11, 14, 17- icosapentaenoate

Molecular formula:
$C_{22}H_{34}O_2$

Molecular weight:
330.51

Structural formula:

Description:
Ethyl icosapentate is colorless to pale yellow, clear liquid. It has a faint characteristic odor and taste. It is miscible with methanol, with ethanol, with acetone, with ether, with

chloroform or with hexane, and practically insoluble in water.

PACKAGING

Capsules: Boxes of 100, 500, 1,000 and 1,050 in press-through packages

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23) Yamaguchi, K. et al.: Prostaglandins Leukotrienes Med. 28, 35-43 (1987)
24) Mizota, M. et al.: Folia Pharmacol. Japon 91 (2), 81-89 (1988)

REQUEST FOR LITERATURE SHOULD BE MADE TO:

Marketing and Scientific Division
Mochida Pharmaceutical Co., Ltd.
7, Yotsuya 1-chome, Shinjuku-ku, Tokyo 160-8515, Japan
TEL (03)3358-7211 FAX (03)5229-3955

INFORMATION ON LONG-TERM ADMINISTRATION

This product may be prescribed for a single period of up to 30 days in accordance with Notification No.26, issued on March 8, 1996 by the Ministry of Health and Welfare of Japan.

Manufactured and Distributed by:
MOCHIDA Pharmaceutical Co., Ltd.
7, Yotsuya 1-chome, Shinjuku-ku, Tokyo 160-8515, Japan

Revised: January 2007 (8th version)

Standard Commodity Classification No. of Japan
873399
872189

• An EPA Preparation •

EPADEL® S 300
EPADEL® S 600
EPADEL® S 900

< JP Ethyl Icosapentate, Soft Capsules >

Designated drug

Storage
Store at room temperature.

Expiration date
This drug should be used before the expiration date indicated on the package.

	300 mg	600 mg	900 mg
Approval No.	21000AMZ00809000	21000AMZ00810000	21600AMZ00409000
Date of listing in the NHI reimbursement price	December 1998	December 1998	June 2004
Date of initial marketing in Japan	January 1999	January 1999	July 2004

CONTRAINDICATIONS (EPADEL S is contraindicated in the following patients.)

Hemorrhaging patients (e.g. hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, vitreous hemorrhage, etc.) [Hemostasis may be more difficult.]

DESCRIPTION

Brand name	EPADEL S 300	EPADEL S 600	EPADEL S 900
Ingredient/ content	300 mg of JP ethyl icosapentate per pack	600 mg of JP ethyl icosapentate per pack	900 mg of JP ethyl icosapentate per pack
Inactive ingredients	Tocopherol		
	Capsule composition	Gelatin D-Sorbitol Concentrated glycerin ethyl parahydroxybenzoate propyl parahydroxybenzoate	
Dosage form	Pale yellow, clear, soft capsules		
Appearance	Spherical shape with a diameter of approximately 4 mm		
Identification code (Labeled on packs)	MO 209	MO 20A	MO 20D

INDICATIONS
DOSAGE AND ADMINISTRATION

Indications	Dosage and Administration
Improvement of the associated ulcer, pain and coldness in arteriosclerosis obliterans	Usually for adults, administer orally 600 mg of ethyl icosapentate 3 times daily, immediately after meals. The dose may be increased or decreased, depending on the age and condition of the patient.
Hyperlipidemia	Usually for adults, administer orally 600 mg of ethyl icosapentate 3 times daily, immediately after meals. In the case that triglyceride level is abnormal, the dose may be increased up to 900 mg 3 times daily, depending on severity.

PRECAUTIONS

1. Careful Administration (EPADEL S should be administered with care in the following patients.)
   (1) Patients in menstruation
   (2) Patients with hemorrhagic tendency
   (3) Patients scheduled for surgery
   [(1)-(3) Hemorrhage may be exacerbated.]
   (4) Patients on medication with anticoagulants or antiaggregators of platelets (See "Drug Interactions")

2. Important Precautions
   (1) To use EPADEL S for improvement of the associated ulcer, pain and coldness in arteriosclerosis obliterans, observe the course closely, and if the drug is not responded to, discontinue the use of the drug and

switch to another therapy. It is also advisable to perform periodical hematologic testing during the administration of EPADEL S.

(2) To use EPADEL S for Hyperlipidemia, the following should be taken into consideration:

1) Use of EPADEL S should be considered only after hyperlipidemia has been established by a thorough examination.
2) Prior to EPADEL S therapy, diet therapy, fundamental treatment for hyperlipidemia, should be given, and an exercise therapy and a reduction of ischemic heart disease risks, such as hypertension and smoking should be considered.
3) During the treatment, the blood lipid level should be measured periodically. If no response to the treatment is obtained, the EPADEL S therapy should be discontinued.

3. Drug Interactions

Precautions for coadministration (EPADEL S should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Anticoagulants (e.g. warfarin, etc.) Antiaggregators of platelets (e.g. aspirin, indomethacin, ticlopidine hydrochloride, cilostazol, etc.)	Hemorrhagic tendency may be increased.	Since ethyl icosapentate has an anti-platelet effect, coadministration with anticoagulants and antiaggregators of platelets may increase hemorrhagic tendency.

4. Adverse Reactions

Adverse reactions were observed in 647(4.4%) of 14,605 patients treated. (EPADEL Capsules 300 and EPADEL S 300/600 data (hyperlipidemia) at the date of application of reexamination)

Adverse Reaction

If the following adverse reactions are observed, appropriate measures should be taken in accordance with the symptoms of the patients.

	5% ≥ ≥0.1%	<0.1%	Incidence unknown
Hypersensitivity *1)	Rash,itching, etc.		
Hemorrhagic tendency *2)		Subcutaneous hemorrhage, hematuria, gingival bleeding, ocular fundus bleeding, epistaxis, gastrointenstinal bleeding, etc.	
Hematologic	Anemia,etc.		
Gastrointestinal	Nausea, abdominal discomfort, diarrhea, abdominal pain, heartburn	Vomiting, anorexia, constipation, stomatitis, thirst, abdomen enlarged feeling, etc.	
Hepatic *2)	Hepatic dysfunction with increased AST (GOT), ALT (GPT), Al-P, γ-GTP and LDH		Jaundice
Renal		Increased BUN, increased creatinine	
Respiratory *2)		Cough	Dyspnea
Others	Increased CK (CPK)	Headache, dull, dizziness, giddiness, sleepiness, insomnia, hot flush, feeling of warmth, fever, palpitations, edema, numbness, arthralgia, pollakiuria, increased uric acid, general malaise	Gynecomastia

Note 1) If there is any such manifestation, discontinue the use of EPADEL S.
2) Observe the patient closely, and if any such manifestation occurs, discontinue the use of EPADEL S and appropriate measures must be taken.

5. Use during Pregnancy, Delivery or Lactation

(1) As the safety of EPADEL S in pregnancy has not been established, administer EPADEL S to pregnant women or women suspected to be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

(2) It is advisable not to administer the drug to nursing women, but when administration is judged necessary women should be advised to stop nursing. [Animal studies (rats) have shown that EPADEL S is excreted in breast milk.]

6. Pediatric Use

The safety of EPADEL S in children has not been established. (No clinical experience.)

7. Precautions concerning Use

Cautions for use

(1) As EPADEL S, if administered on an empty stomach, is poorly absorbed, administer the capsules immediately after meals.

(2) Do not chew the capsules.

8. Other Precautions

It has been reported that in case of the patient with a poorly controled high blood presure, when co-administered with other antiplatelet agents, the cerebral hemorrhage occured.

PHARMACOKINETICS

1. Plasma levels

Oral administration of a single dose of 2,700 mg of EPADEL S to healthy adult men immediately after a meal was followed by the occurrence of a peak plasma level of the drug 6 hours later. Daily oral administration of 600 mg or 900 mg of EPADEL Capsules 300 3 times a day for 4 weeks, immediately after meals, resulted in the plasma level of EPADEL Capsules 300 reaching a plateau in about one week from the first administration.

Note) The approval single dosage of EPADEL S is up to 900 mg.

2. Excretion (reference)

Oral administration of ^{14}C-EPA-E to male rats was followed by urinary excretion of 2.7% and the fecal excretion of 16.7% of the administered dose during 168 hours after the administration. Also, 44.4% of the administered radioactivity was excreted in the expired air. [1]

CLINICAL STUDIES

•Data of EPADEL S 300/600

The overall improvement rate of hyperlipidemia in clinical studies[2,3] was such that the effectiveness as "moderately to remarkably improved" was 47.5% (19/40 patients).

•Data of EPADEL Capsules 300 (reference)

1. Arteriosclerosis obliterans

In clinical studies[4-7] of EPADEL Capsules 300 including double-blind comparative studies, the effectiveness of the drug in treating patients with arteriosclerosis obliterans, associated with ulcer, resting pain and coldness due to peripheral circulatory disorder, was such that the effectiveness as "remarkably effective" was 55.9% (52/93 patients), and the effectiveness as "fairly to remarkably effective" was 88.2% (82/93 patients).

2. Hyperlipidemia

In clinical studies[8-12] of EPADEL Capsules 300 including double-blind comparative studies, the overall improvement rate of the drug in treating patients with hyperlipidemia, was such that the effectiveness as "remarkably improved" was 43.8% (163/372 patients), and the effectiveness as "fairly to remarkably improved" was 68.0% (253/372 patients).

In long term administration studies (24-52 weeks)[9-12] total serum cholesterol (before administration, higher than 220mg/dL, 137 patients) decreased 3-6%, and serum triglyceride (before administration, higher than 150mg/dL, 97 patients) decreased 14-20%, thus, indicating the drug's efficicy in reducing these levels.

PHARMACOLOGY

1. Serum lipids-lowering effect

(1) EPA-E significantly decreases total serum cholesterol level and/or serum triglyceride level of hyperlipidemic patients.[8-14]

(2) The effect of decreasing blood lipid levels is shown in hyperlipidemic animals (rats, rabbits) fed on high-cholesterol food, hyperlipidemic rats fed on food including casein or fed on triton and in animals (rats, hamsters) fed on normal food.[15-17]

(3) When EPA-E is administered orally to rats, EPA content in lipoprotein increases and the elimination of lipoprotein in blood is enhanced.[18,19]

(4) EPA-E inhibits the intestinal cholesterol absorption and the hepatic cholestrol biosynthesis, and also enhances hepatic biliary secretion(rats).[18]

(5) EPA-E inhibits the intestinal triglyceride absorption, the hepatic triglyceride biosythesis, the hepatic secretion, and also increases the plasma lipoprotein lipase activation (rats).[19,20]

2. Anti-platelet effect

(1) EPA-E inhibits the platelet aggregation induced by various platelet aggregators, and, likewise, inhibits platelet viscosity in patients with various thrombotic and arteriosclerotic diseases.[14]

(2) It appears that EPA-E inhibits competitively the metabolism of arachidonic acid released from the platelet membrane, chiefly by increasing the EPA content of phospholipids in the platelet membrane thereby inhibiting the formation of thromboxane A_2 and consequently inhibiting platelet aggregation.[21]

(3) EPA-E inhibits the platelet aggregation induced by collagen (rabbits, *ex vivo*).[21]

(4) EPA-E inhibits the platelet aggregation induced by collagen, ADP or arachidonic acid in rats, rabbits and humans (*in vitro*).[21]

(5) EPA-E has proved not to change or to increase the formation of prostacyclin-like substances in the walls of rat thoracic aorta.[22]

3. Arterial elasticity-maintaining effect

(1) EPA-E inhibits the decreased elasticity of isolated aorta from rabbits fed on high-cholesterol food, keeping the aorta as elastic as those from rabbits fed on normal food.[23]

(2) EPA-E inhibits the increase in pulse wave velocity (PWV) in the thoracic aorta and the femoral artery of rabbits fed on high-cholesterol food to the extent that it is comparable to the velocity in the rabbits fed on normal food.[24]

(3) EPA-E inhibits the decrease of density of medial smooth muscle cells, decrease of elastin content, and the accumulation of free cholesterol in the smooth

muscle of aorta specimens prepared from rabbits fed on high-cholesterol food.[24] EPA-E also inhibits the proliferation of the intimal smooth muscle cells.

4. Effects on models for various pathologic conditions
EPA-E, when administered orally, prevents the sudden death due to a formation of thrombus by intravenous injection of arachidonic acid (rats).[23] It also inhibits the formation of thrombus in thrombotic occulson due to arteriovenous shunting (rats)[25] and in ellagic acid-induced thrombosis (rabbits)[20], and also prevents the progress of peripheral gangrene (rats) induced by lauric acid.[26]

PHYSICOCHEMISTRY

Nonproprietary name:
Ethyl icosapentate (JAN), Icosapent (INN)

Chemical name:
Ethyl (5Z, 8Z, 11Z, 14Z, 17Z) - icosa - 5, 8, 11, 14, 17 - pentaenoate

Molecular formula:
$C_{22}H_{34}O_2$

Molecular weight:
330.50

Structural formula:

Description:
Ethyl icosapentate is colorless to pale yellow, clear liquid. It has a faint characteristic odor. It is miscible with ethanol (99.5), with acetic acid (100), with hexane, and practically insoluble in water or in ethylene glycol.

PACKAGING

300 mg: 84 packs, 420 packs
600 mg: 84 packs, 420 packs
900 mg: 84 packs, 420 packs

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